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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
CHEN, S	
ART UNIT	**PAPER NUMBER**
1633	20

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/258,217	Applicant(s) KEATING ET AL.	
	Examiner Shin-Lin Chen	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *18* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

In view of the amendment filed 6-1-01, the finality of Official action filed 1-3-01 (Paper No. 13) has been withdrawn.

The amendment filed 6-1-01 has been entered. Claims 1, 3, 5, 9 and 10 have been amended. Claims 1-6, 9 and 10 are pending.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See M.E.P.. § 2172.01. The omitted steps are: the activity of elastase of **what** is intended; is a human cell, a mouse cell, a human, or an ELN transgenic mouse intended to be used for the drug candidate? What is contacted by the drug candidate for the screening method?

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 2, 5, 6, 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making an ELN+/- mouse having increased number of elastic lamellae and ELN-/- mouse having arterial occlusion, does not reasonably provide enablement for making any ELN +/- mouse having various phenotypes other than the disclosed ELN +/- and ELN-/- mice, and a method for screening drug candidates useful for treating SVAS, hypertension or atherosclerosis by using said ELN+/- mice. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1 and 2 are directed to a mouse having only one functional elastin gene and with no functional elastin gene, respectively. Claim 5 is directed to a method to screen for drug candidates useful for treating humans with SVAS, hypertension or atherosclerosis, or preventing atherosclerosis by using an ELN +/- mouse or human having only one functional elastin gene, wherein said drug candidates inhibit occlusion of arteries. Claim 6 is directed to a method to screen for drug candidates useful for treating humans with SVAS, hypertension or atherosclerosis, or preventing atherosclerosis by measuring the activity of elastase in the presence of drugs wherein said drugs which inhibit elastase are said drug candidates. Claims 9 and 10 are

directed to a method to screen for drug candidates useful for treating humans with SVAS, hypertension or atherosclerosis by using ELN +/- mouse or human or ELN +/- cells having only one functional elastin gene and by measuring the synthesis of elastin mRNA or synthesis of elastin.

The specification discloses the generation of ELN +/- mice having 47% decrease in ELN mRNA and 50% thinner in elastic lamallae as compared to ELN +/+ mice, and ELN-/- mice having arterial occlusion and the ELN-/- mice were dead by P4.5. The specification fails to provide an enabling disclosure for the preparation of ELN +/- and ELN-/-mice having various phenotypes except ELN +/- and ELN-/- mice as disclosed, because it fails to provide sufficient guidance for the preparation of ELN transgenic mice other than the disclosed ELN transgenic mice and further because it fails to provide a suitable description of the ELN +/- mice used for the claimed method. No teachings are present within the specification in regard to how one would have prepared any ELN +/- or ELN-/- mouse having a predictable phenotype as shown in applicant's ELN +/- or ELN-/- mice without the skilled practitioner having to engage in undue experimentation to practice the invention over the full scope claimed.

The state of the art in the field of transgenics at the time of the invention was unpredictable. Transgene expression and phenotypic/physiological results of such expression is not always accurately predictable and the phenotype of a transgenic knockout organism is unpredictable. Houdebine, 1994 (U2) points out that transgene expression in transgenic animal is heavily dependent on its site of integration in the host genome rather than on the number of

copies, the site of integration of a gene is unpredictable and thus the expression of a transgene in a given animal is unpredictable when the DNA is microinjected into the pronuclei by the conventional method (e.g. p. 277). Seamark, 1994 (V2) points out that even pig's pluripotent ES cells can be created, no group has demonstrated totipotency of these cells through reinstating their genome within a germ line, and procedures for reinstating the ES cell genome into a germ line are still far from routine. Small changes in the environment the embryo is exposed to can impact on development with long-term implications on health and warefare. For example, in the mouse, brief exposure of preimplantation embryos to *in vivo* culture conditions can both result in substantial phenotypic variation and predicate the subsequent expression and penetration of some transgenes. Asynchrony between the stage of development of the embryo and tract at embryo transfer can also affect development (e.g. p. 654, 655).

Wu et al., 1997 (Methods in Gene Biotechnology, CRC Press, Boca Raton, p. 339-365) pointed out that the approach of using ES cells carrying a single-copy mutation of a specific gene to generate knockout transgenic animal is time-consuming and costly to obtain homozygous or double-knockout mice, and another major concern is the potentially lethal effect of the targeted gene. In some cases, gene knockout results in early death of embryos and young animals, or morphologically and functionally abnormal offsprings such as blind and/or handicapped animals (e.g. p. 340). Anders et al. (2000, Experimental Nephrology, Vol. 8, No. 4-5, pp. 181-193) reports that "the phenotype of many disease models is rather strain specific and depends on the genetically determined immune response after a certain stimulus...The problem of an undefined

genetic background in transgenes also includes the lack of adequate controls. Because of marked polymorphism in the genetic background of many laboratory mouse strains, it cannot be concluded that the null mutations is the only cause for a phenotypical change" (e.g. page 182) and "As the genetic background is of such importance for transgenic studies, reproducible models of renal disease with a well-defined genetic background are essential" (e.g. p. 183). Further, Bradley et al., 1992 (Biotechnology, Vol. 10, p. 534-539) reports that when a targeting vector, used to generate null alleles, is introduced into an ES cell it may follow two different integration pathways, either into a random chromosomal site or into its homologous site in the genome. "Generally, the frequency of targeted integration events is lower than random integration events by several orders of magnitude. The ratio of targeted to random integration events is important...There are many factors that may influence this ratio some of which are: the length of homology, the target locus, the use of an insertion or replacement vector, and the degree of polymorphic variation between the vector and the target" (e.g. page 536, left column). In view of the unpredictability of the resulting phenotypes of the ELN transgenic knockout mice, the importance of the genetic background of the mice for transgenic studies, and various factors that can influence the resulting transgenic mice, one skilled in the art at the time of the invention would not know how to use the claimed ELN transgenic knockout mice and would have to engage in undue experimentation to practice over the full scope of the invention claimed.

Further, The specification fails to provide adequate guidance and evidence that a drug candidate that inhibits elastase activity would provide therapeutic effects in **treating** humans

with atherosclerosis, SVAS or essential hypertension or **preventing** atherosclerosis in humans. No correlation between the inhibition of elastase activity and treating humans with atherosclerosis, SVAS or essential hypertension or preventing atherosclerosis in humans has been provided. The rationale of inhibiting elastase activity would reduce the metabolism of elastin by elastase fails to provide sufficient correlation between the inhibition of elastase activity and treating humans with atherosclerosis, SVAS or essential hypertension or preventing atherosclerosis in humans. It is unclear whether the inhibition of elastase activity would increase the elastin gene expression or elastin activity *in vivo* in a subject. No direct evidence has been shown in the specification that a drug candidate inhibiting elastase activity *in vivo* would be useful in providing therapeutic effect for treating humans with atherosclerosis, SVAS or essential hypertension or preventing atherosclerosis *in vivo*. Thus, one skilled in the art would not know how to use the claimed invention and would require undue experimentation to practice over the full scope of the invention claimed.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to have made and used the full scope of the claimed inventions. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sechler et al., 1995 (U) in view of Morris, 1998 (Current Opinion in Cardiology, Vol. 13 (3), p. 214-219) and Wydner et al., 1994 (X2).

Claims 1 and 3 are directed to a mouse or a mouse cell comprising one functional mouse elastin gene and either one nonfunctional or no second mouse elastin gene in its genome. Claims 2 and 4 are directed to a mouse or a mouse cell comprising a genome with no functional elastin gene.

Sechler teaches construction of transgenic mice that contain rat tropoelastin gene (elastin gene) lacking exon sequences within the 5' or 3' end of the gene, e.g. lacking exon 33 or exons 19-31 (e.g. p. 151, 152). The transgenic mice disclosed by Sechler et al. includes hemizygous ELN +/- and homozygous ELN -/-. The mice set forth above contain mouse cells comprising a genome with no functional elastin gene. Sechler also teaches that there are a variety of disorders characterized by abnormal elastin synthesis and a concomitant deposition of aberrant elastic fiber, such as hypertension, atherosclerosis, actinic elastosis, Marfan's syndrome and SVAS, and mutations in the tropoelastin gene (elastin gene) plays a role in analogous human disorders of

elastic tissue, including SVAS (e.g. p. 149). Sechler teaches using the transgenic mice having mutated elastin gene to study the role of elastin gene in analogous human disorder such as SVAS.

Sechler does not teach the availability of mouse elastin gene for making a mouse containing mutated mouse elastin gene and making a mouse lacking one or both endogenous elastin gene.

Morris teaches that "Individuals with Williams syndrome are hemizygous for the elastin gene, owing to a 1 to 2 megabase deletion of a portion of the long arm of chromosome 7 that encompasses ELN... The severity of SVAS is quite variable, both in series of Williams syndrome patients and within SVAS kindreds, suggesting that other genetic factors are involved in expression of the phenotype. Experiments with elastin knockout mice will likely yield clues regarding the role of elastin in arterial morphogenesis and the pathogenesis of obstructive vascular disease" (e.g. abstract).

Wydner teaches the complete cDNA sequence of mouse tropoelastin (elastin) gene and the mutations in the tropoelastin gene are strongly implicated in supravalvular aortic stenosis (SVAS), a heritable vascular disorder that maps to chromosome 7 (e.g. introduction, p. 128, 129).

It would have been obvious for one of ordinary skill in the art at the time of the invention to substitute the rat elastin gene with a mouse elastin gene as taught by Wydner to make homozygous or heterozygous transgenic mice or mouse cells having mutated endogenous mouse elastin gene as taught by Sechler and Morris.

One having ordinary skill at the time the invention was made would have been motivated to produce heterozygous or homozygous transgenic mice or mouse cells having mutated endogenous mouse elastin gene in order to study the role of elastin gene in arterial morphogenesis, the pathogenesis of obstructive vascular disease, and in analogous human disorder such as SVAS because Morris teaches that SVAS is the result of mutation or deletion of the elastin (ELN) gene and experiments with elastin knockout mice will likely yield clues regarding the role of elastin in arterial morphogenesis and the pathogenesis of obstructive vascular disease.

Applicants argue that the claimed mice and cells are not drawn to mice or mouse cells comprising a mutated gene plus a wild type gene as taught by Sechler, but rather are drawn to mice and cells that are deficient in elastin. Applicants further argue that Sechler states that it was not known if the disruption of the elastin gene cause the SVAS phenotype and does not provide motivation for the claimed invention (amendment, page 5-6). This is not found persuasive because of the teachings of Morris as discussed above. Morris teaches that SVAS is the result of mutation or deletion of the elastin (ELN) gene and experiments with elastin knockout mice will likely yield clues regarding the role of elastin in arterial morphogenesis and the pathogenesis of obstructive vascular disease. Thus, Morris provide motivation to practice the invention claimed in the present application.

8. Claims 5, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reitamo et al., 1994 (V) in view of Sechler et al., 1995 (U), Morris, 1998 (Current Opinion in Cardiology, Vol. 13 (3), p. 214-219) and Wydner et al., 1994 (X2).

Claim 5 is directed to a method to screen for drug candidates useful for treating humans with SVAS, hypertension or atherosclerosis by using an ELN +/- mouse or human, wherein said drug candidates inhibit occlusion of arteries. Claims 9 and 10 are directed to a method to screen for drug candidates useful for treating humans with SVAS, hypertension or atherosclerosis by using ELN +/- mouse or human, or ELN +/- mouse or human cells and by measuring the synthesis of elastin RNA and elastin, respectively.

Reitamo teaches generating transgenic mice expressing a human elastin promoter/CAT reporter gene construct and injecting IL-10 subcutaneously into said transgenic mice. Reitamo et al. also teach a method of screening a compound which can stimulate the elastin promoter *in vivo or in vitro,* and show IL-10 up-regulates elastin gene expression *in vivo* by CAT assay (transgenic mice skin) and *in vitro* by measuring the elastin mRNA level using Northern analysis (e.g. abstract, p. 332).

Reitamo does not teach using ELN +/- mice or ELN +/- cells to screen drug candidate useful for treating atherosclerosis hypertension or SVAS in a human by measuring the synthesis of elastin or screen drug which inhibits occlusion of arteries.

Sechler teaches construction of transgenic mice that contain rat tropoelastin gene (elastin gene) lacking exon sequences within the 5' or 3' end of the gene, e.g. lacking exon 33 or exons

19-31 (e.g. p. 151, 152). The transgenic mice disclosed by Sechler includes hemizygous ELN +/- and homozygous ELN -/-. The mice set forth above contain mouse cells comprising a genome with no functional elastin gene. Sechler also teaches that there are a variety of disorders characterized by abnormal elastin synthesis and a concomitant deposition of aberrant elastic fiber, such as hypertension, atherosclerosis, actinic elastosis, Marfan's syndrome and SVAS, and mutations in the tropoelastin gene (elastin gene) plays a role in analogous human disorders of elastic tissue, including SVAS (e.g. p. 149). Sechler teaches using the transgenic mice having mutated elastin gene to study the role of elastin gene in analogous human disorder such as SVAS.

Morris teaches that "Individuals with Williams syndrome are hemizygous for the elastin gene, owing to a 1 to 2 megabase deletion of a portion of the long arm of chromosome 7 that encompasses ELN... The severity of SVAS is quite variable, both in series of Williams syndrome patients and within SVAS kindreds, suggesting that other genetic factors are involved in expression of the phenotype. Experiments with elastin knockout mice will likely yield clues regarding the role of elastin in arterial morphogenesis and the pathogenesis of obstructive vascular disease" (e.g. abstract).

Wydner teaches the complete cDNA sequence of mouse tropoelastin (elastin) gene and the mutations in the tropoelastin gene are strongly implicated in supravalvular aortic stenosis (SVAS), a heritable vascular disorder that maps to human chromosome 7 (e.g. introduction, p. 128, 129).

It would have been obvious for one of ordinary skill in the art at the time of the invention to substitute the rat elastin gene with a mouse elastin gene as taught by Wydner to make homozygous or heterozygous transgenic mice or mouse cells having mutated mouse elastin gene as taught by Sechler and Morris. Morris teaches that the mutation of elastin gene is associated with SVAS, an inherited obstructive vascular disease that affects the aorta, carotid, coronary and pulmonary arteries. It would have been obvious for one of ordinary skill to use the ELN +/- mice or ELN +/- mouse cells as taught by Wydner, Morris and Sechler to screen for drugs or compounds useful for treating humans with SVAS, hypertension or atherosclerosis which are diseases associated with arteries.

One having ordinary skill at the time the invention was made would have been motivated to produce heterozygous or homozygous transgenic mice or mouse cells having mutated endogenous mouse elastin gene in order to study the role of elastin gene in arterial morphogenesis, the pathogenesis of obstructive vascular disease, and in analogous human disorder such as SVAS because Morris teaches that SVAS is the result of mutation or deletion of the elastin (ELN) gene and experiments with elastin knockout mice will likely yield clues regarding the role of elastin in arterial morphogenesis and the pathogenesis of obstructive vascular disease. One having ordinary skill at the time the invention was made would have been motivated to use the ELN +/- mice or mouse cells as taught by Wydner, Morris and Sechler to screen for drugs or compounds useful for treating SVAS, atherosclerosis or hypertension in a human by measuring the synthesis of elastin mRNA or elastin, or the drug or compound which

can inhibit the occlusion of arteries because the implication of the correlation of SVAS, hypertension and atherosclerosis with the elastin gene as taught by Sechler, Morris, and the discovery of such compounds would have been useful for treating humans with SVAS, hypertension or atherosclerosis.

Conclusion

No claims is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Kimberly Davis, whose telephone number is (703) 305-3015.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Deborah Clark

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